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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,449,470

APPLICATION NO.: 10/574,436

ISSUE DATE : November 11, 2008

INVENTOR(S) : Lisa Chung Wai Chang, Adriaan P. Ijzerman, Johannes Brusse

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column	Line	Error	Correct to Read
15	37	desired product. 1 H NMR δ (DMSO-d6):	desired product. ^{1}H NMR δ (DMSO-d6):
16	41	($C_{18}H_{15}N_3O.0.5.O.EtOH$), C, H, N.	($C_{18}H_{15}N_3O.0.5.0.EtOH$), C, H, N.
17	33	6H, J=7.31 Hz, $CH(CH_2CH_3)2$)ppm.	6H, J=7.31 Hz, $CH(CH_2CH_3)_2$)ppm.
18	52	13 $C_{23}H_{17}N_3O\bullet25H_2O$ Calc.	13 $C_{23}H_{17}N_3O.0.25H_2O$ Calc.
18	54	14 $C_{18}H_{15}N_3O\bullet0.5EtOH$.	14 $C_{18}H_{15}N_3O.0.5EtOH$.
18	58	16 $C_{20}H_{19}N_3O\bullet0.14H_2O$	16 $C_{20}H_{19}N_3O.0.14H_2O$
18	60	17 $C_{20}H_{19}N_3O\bullet0.1H_2O$	17 $C_{20}H_{19}N_3O.0.1H_2O$
18	64	19 $C_{22}H_{23}N_3O\bullet0.1H_2O$	19 $C_{22}H_{23}N_3O.0.1H_2O$
19	10	23 $C_{21}H_{19}N_3O\bullet0.01H_20$	23 $C_{21}H_{19}N_3O.0.01H_20$
19	12	24 $C_{22}H_{23}N_3O\bullet0.04H_20$	24 $C_{22}H_{23}N_3O.0.04H_20$

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Column	Line	Error	Correct to Read
19	14	25 $C_{23}H_{23}N_3O\bullet 0.15H_2O$	25 $C_{23}H_{23}N_3O.0.15H_2O$
19	43	substuents are varied.	substituents are varied.
20	65	Potent A Adenosine Receptor Antagonists.	Potent A_3 Adenosine Receptor Antagonists.

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(12) United States Patent
Chang et al.

(10) Patent No.: US 7,449,470 B2
(45) Date of Patent: Nov. 11, 2008

(54) **SUBSTITUTED PYRIMIDINES AS LIGANDS OF ADENOSINE RECEPTORS**

(75) Inventors: **Lisa Chung Wai Chang**, Sydney (AU); **Adriaan P. Ijzerman**, Haarlem (NL); **Johannes Brussee**, Rijnsburg (NL)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 70 days.

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PCT Pub. Date: **Apr. 14, 2005**

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(51) **Int. Cl.**

C07D 239/42	(2006.01)
A61K 31/505	(2006.01)
A61P 9/00	(2006.01)
A61P 11/00	(2006.01)
A61P 25/00	(2006.01)
A61P 35/00	(2006.01)

(52) **U.S. Cl.** **514/256**; 544/326; 544/329

(58) **Field of Classification Search** 544/326, 544/329; 514/275, 256

See application file for complete search history.

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(Continued)

Primary Examiner—Venkataraman Balasubram
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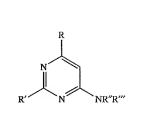
(57) **ABSTRACT**

The invention provides a compound of formula (I) wherein R and R' are selected from hydrogen, alkyl, alkenyl, alkynyl, or aryl; R" and R'" are selected from hydrogen, acyl, thio-acyl, seleno-acyl, alkyl, alkenyl, alkynyl, or aryl; or a pharmaceutically acceptable salt thereof, to interact with the adenosine receptors in the beneficial treatment and/or prevention of a (dis)order arising from the said receptors. The invention further provides pharmaceutical compositions comprising said compounds. The invention also relates to the use of said compositions for treating an/or preventing a variety of diseases.

(I)



5 Claims, No Drawings

Chemistry—General

Chemicals and Solvents All reagents were obtained from commercial sources and all solvents were of an analytical grade.

Chromatography Thin-layer chromatography (TLC) was carried out using Merck silica gel plastic backed F_{254} plates, visualised under UV (254 nm).

Instruments and Analysis Elemental analyses were performed for C,H,N (Leiden Institute of Chemistry, Leiden University, The Netherlands). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^1H NMR, 200MHz; ^{13}C NMR, 50.29 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ) relative to this. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Mass Spectra were measured on a Finnigan MAT TSQ-70 spectrometer equipped with an electrospray interface for ESI experiments. Spectra were collected by constant infusion of the analyte dissolved in methanol. ESI is a soft ionisation technique resulting in protonated, sodiated species in positive ionisation mode and deprotonated species in the negative ionisation mode.

Synthetic Procedures

2,6-Diphenyl-3H-pyrimidin-4-one (10)[7]

Benzamidine hydrochloride (3.9 g, 24.9 mmol) was dissolved in a minimal amount of H_2O (10 mL), to this was added sodium hydroxide pellets (1.0 g, 24.9 mmol, 1 eq.) dissolved in H_2O (2 mL), followed by ethylbenzoate (4.53 mL, 26.1 mmol, 1.05 eq.). Ethanol was then added until a clear solution was obtained. The reaction mixture was then allowed to stir at room temperature overnight yielding a thick suspension, which was then filtered to give a white solid. After washing with diethyl ether to remove unreacted/excess β-ketoester the solid was dried in vacuo to give 57% of the desired product. ^1HNMR δ (DMSO-d6): 8.31-8.18 (m, 5H, Ar), 7.60-7.54 (m, 5H, Ar), 6.92 (s, 1H, Ar). ↳ 1H

4-Chloro-2,6-diphenyl-pyrimidine (11)[8]

Phosphorous oxychloride (9.30 mL, 99.8 mmol, 7.5 eq.) was added dropwise to 2,6-diphenyl-3H-pyrimidin-4-one (10) (3.3 g, 13.3 mmol) in a vigorous reaction. To this mixture was added slowly phosphorous pentachloride (2.77 g, 13.3 mmol, 1 eq.) and the reaction mixture was stirred at reflux for 3 hours. The reaction mixture was then quenched by pouring into ice-water, and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated to give a yellow solid. This was recrystallised from hot ethanol to give fine white needles (65%). ^1H NMR δ ($CDCl_3$): 8.60-8.18 (m, 5H, Ar), 7.63 (s, 1H, Ar), 7.51-7.57 (m, 5H, Ar).

2,6-Diphenyl-pyrimin-4-ylamine (12)

Ethanol (50 mL) was saturated with NH_3(g) at 0° C. and added to 4-chloro-2,6-diphenyl-pyrimidine (11) (2.30 g, 8.63 mmol) in a sealed vessel. This was then stirred at 140° C. for 24 h. Upon cooling and concentrating, the residues were extracted with hot chloroform (3×50 mL) and the solvent evaporated in vacuo. The crude product was purified by column chromatography on SiO_2 eluting with CH_2Cl_2 to give an off-white solid (80%). ^1H NMR δ (DMSO-d6): 8.47-8.42 (m, 2H, Ar), 8.16-8.13 (m, 2H, Ar), 7.57-7.5 (m, 6H, Ar), 7.02 (br s, 2H, NH_2), 6.88 (s, 1H, Ar).

General Procedure for the Preparation of 4-Amido-2,6-diphenylpyrimidines (13-25)

To a solution of 4-amino-2,6-diphenylpyrimidine (0.202 mmol, 1 eq.) in 1,4-dioxane (5 mL) was added triethylamine (0.223 mmol, 1.1 eq.), followed by the appropriate acid chloride (0.304 mmol, 1.5 eq.). This was then stirred at reflux until no starting material was visible by TLC. Upon completion, the reaction mixture was separated between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was further extracted with ethyl acetate (2×20 mL) and the combined organics washed with water and brine. After drying over $MgSO_4$ and evaporation under reduced pressure, the crude product was purified by column chromatography, eluting with a petroleum ether-ethyl acetate or a dichloromethane-methanol solvent system. Recrystallisation with ethanol or petroleum ether-ethyl acetate gave the corresponding amide in crystalline form.

N-(2,6-Diphenyl-pyrimidin-4-yl)-benzamide (13).

Yield 48%; white solid; mp 120-123° C.; ^1H NMR δ ($CDCl_3$): 8.78 (bs, 1H, N—H), 8.72 (s, 1H, pyrimidine-H), 8.58-8.54 (m, 2H, phenyl-H), 8.34-8.29 (m, 2H, phenyl-H), 7.99-7.96 (m, 2H, phenyl-H), 7.64-7.48 (m, 9H, phenyl-H). ^{13}C-NMR δ ($CDCl_3$): 166.2, 165.9, 164.0, 158.4, 137.3, 137.1, 133.4, 132.6, 130.8, 130.7, 128.9, 128.7, 128.3, 128.1, 127.4, 127.2, 103.3. MS (ES+): 351.57, 373.55 Da. Anal. ($C_{23}H_{17}N_3O.0.25H_2O$) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-acetamide (14).

Yield 43%; white solid; mp 140° C.; ^1H NMR δ ($CDCl_3$): 8.54-8.49 (m, 3H, phenyl-H+ pyrimidinyl-H) 8.45 (s, 1H, N—H), 7.55-7.49 (m, 6H, phenyl-H), 2.20 (s, 3H, CH_3)ppm. ^{13}C-NMR δ ($CDCl_3$): 165.9, 158.1, 154.3, 140.7, 130.74, 130.68, 128.7, 128.4, 128.0, 127.4, 103.0, 35.7ppm. MS (ES^+): 289.89 Da. Anal. ($C_{18}H_{15}N_3O.0.50EtOH$) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-propionamide (15).

Yield 77%; white solid; mp 125-126° C.; ^1H-NMR δ ($CDCl_3$): 8.58 (s, 1H, pyrimidinyl-H), 8.55-8.50 (m, 2H, phenyl-H), 8.36 (bs, 1H, NH), 8.30-8.25 (m, 2H, phenyl-H), 7.54-7.49 (m, 6H, phenyl-H), 2.41(q, 2H, J=7.3 Hz, CH_2CH_3), 1.23 (t, 2H, $—CH_2CH_3$)ppm. ^{13}C-NMR δ ($CDCl_3$): 173.2, 165.8, 163.9, 137.3, 137.0, 130.7, 128.7, 128.0, 127.4, 121.5, 103.1, 30.7, 8.87ppm. MS (ES^+): 303.8 Da. Anal. calc. for $C_{19}H_{17}N_3O$ (C 75.23; H 5.65; N 13.85) found (C 75.32; H 6.23; N 14.04)%.

N-(2,6-Diphenyl-pyrimidin-4-yl)-butyramide (16).

Yield 53%; white solid; mp.102-103° C. ^1H-NMR δ ($CDCl_3$): 8.60 (bs, 2H, pyrimidine-H+NH), 8.56-8.51 (m, 2H, phenyl-H), 8.31-8.26 (m, 2H, phenyl-H), 7.45-7.50 (m, 6H, phenyl-H), 2.29 (t, 2H, J=7.48 Hz, $CH_2CH_2CH_3$), 1.71 (sextet, 2H, J=7.39 Hz, $CH_2CH_2CH_3$), 0.95 (t, 3H, J=7.30 Hz, $CH_2CH_2CH_3$)ppm. ^{13}C-NMR δ ($CDCl_3$): 172.9, 165.8, 163.8, 158.5, 137.4, 137.0, 130.8, 130.7, 128.6, 128.4, 128.1, 127.3, 103.3, 39.2, 18.3, 13.5 ppm. MS (ES^+): 317.87 Da. Anal. ($C_{20}H_{19}N_3O.0.14H_2O$) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-isobutyramide (17).

Yield 48%; white solid; mp 116-117° C. ^{1}H-NMR δ ($CDCl_3$): 8.59 (s, 1H, pyrimidine-H), 8.55-8.50 (m, 2H, phenyl-H), 8.30-8.25 (m, 2H, phenyl-H), 8.05 (bs, 1H, NH), 7.54-7.49 (m, 6H, phenyl-H), 2.64 (septet, 1H, J=6.85 Hz, $CH(CH_3)_2$), 1.33 (d, 6H, J=6.94 Hz, $CH(CH_3)_2$)ppm. ^{13}C-NMR δ ($CDCl_3$): 176.5, 165.8, 158.3, 137.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.4, 36.8, 19.2, 19.1 ppm. MS (ES^+): 317.94, 634.75 Da. Anal. ($C_{20}H_{19}N_3O.0.1H_2O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3-methyl-butyramide (18).

Yield 52%, white solid. mp. 127° C. ^{1}H-NMR δ ($CDCl_3$): 8.59 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.35 (bs, 1H, NH), 8.31-8.26 (m, 2H, phenyl-H), 7.56-7.49 (m, 6H, phenyl-H), 2.25-2.24 (m, 3H, $CH_2CH(CH_3)_2$), 1.02-0.99 (d, 6H, $CH_2CH(CH_3)_2$)ppm. ^{13}C-NMR δ ($CDCl_3$): 172.1, 165.9, 158.2, 137.4, 137.1, 130.7, 130.6, 128.6, 128.4, 128.0, 127.4, 113.5, 103.2, 46.8, 25.8, 22.3 ppm. MS (ES^+): 331.8 Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-ethyl-butyramide (19).

Yield 58%, white solid. mp. 137-138° C. ^{1}H-NMR δ ($CDCl_3$): 8.64 (s, 1H, pyrimidine-H), 8.55-8.50 (m, 2H, phenyl-H), 8.31-8.26 (m, 2H, phenyl-H), 8.09 (bs, 1H, NH), 7.54-7.49 (m, 6H, phenyl-H), 2.23-2.11 (m, 1H, $CH(CH_2CH_3)_2$), 1.86-1.56 (m, 4H, $CH(CH_2CH_3)_2$), 0.99 (t, 6H, J=7.31 Hz, $CH(CH_2CH_3)_2$)ppm. ^{13}C-NMR δ ($CDCl_3$): 175.8, 165.9, 158.3, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 121.6, 103.2, 52.2, 25.5, 11.8 ppm. MS (ES^+): 345.86, 690.56 Da. Anal. ($C_{22}H_{23}N_3O.0.1H_2O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-methyl-butyramide (20),

Yield 89%, white solid. mp.: 102° C. ^{1}H-NMR δ ($CDCl_3$): 8.71 (br s, 1H, N-H), 8.67 (s, 1H, pyrimidyl-H), 8.59-8.54 (m, 2H, aromatic-H), 8.33-8.28 (m, 2H, aromatic-H), 7.53-7.50 (m, 6H, aromatic-H), 2.29-2.19 (m, 1H, CH), 1.82-1.86 (m, 1H, 0.5*CH_2), 1.55-1.41 (m, 1H, 0.5*CH_2), 1.16 (d, J=6.58Hz, 3H, CH_3), 0.90 (t, J=7.30 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ ($CDCl_3$): 176.4, 165.9, 163.9, 158.5, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 103.3, 44.0, 27.0, 16.9, 11.6 ppm. MS (ES^+): 331.8 (MH^+) Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2,2-dimethyl-propionamide (21).

Yield 66%, white solid. mp. 52° C. ^{1}H-NMR δ ($CDCl_3$): 8.63 (s, 1H, pyrimidinyl-H), 8.58-8.51 (m, 2H, phenyl-H), 8.30-8.27 (m, 2H, phenyl-H), 8.21 (s, 1H, N—H), 7.54-7.51 (m, 6H, phenyl-H), 1.40 (s, 9H, CH_3)ppm. ^{13}C-NMR δ ($CDCl_3$): 178.0, 165.8, 163.8, 158.4, 137.3, 137.1, 130.7, 130.6, 128.6, 128.3, 128.1, 127.4, 103.2, 40.0, 27.2 ppm. MS (ES^+): 331.92 Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3,3-dimethyl-butyramide (22).

Yield 62%, white solid. mp.: 134° C. ^{1}H-NMR δ ($CDCl_3$): 8.73 (br s, 1H, N—H), 8.64 (s, 1H, pyrimidyl-H), 8.55-8.50 (m, 2H, aromatic-H), 8.32-8.27 (m, 2H, aromatic-H), 7.54-7.49 (m, 11H, aromatic-H), 2.20 (s, 2H, CH_2), 1.08 (s, 9H, 3*CH_3) ppm. ^{13}C-NMR δ ($CDCl_3$): 171.7, 165.9, 163.9, 158.4, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.2, 127.4, 103.2, 51.0. 31.2, 30.0 ppm. MS (ES^+): 367.6 (MNa^+), 345.9 (MH^+) Da. Anal. ($C_{22}H_{23}N_3O$).

Cyclobutanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (23).

Yield 90%, white solid. mp.: 121-122° C. ^{1}H-NMR δ ($CDCl_3$): 8.62 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.32-8.27 (m, 3H, phenyl-H+N—H), 7.54-7.48 (m, 6H, phenyl-H), 3.13 (pentet, 1H, —$CHCH_2CH_2CH_2$—), 2.45-1.90 (m, 6H, —$CHCH_2CH_2CH_2$—)ppm. ^{13}C-NMR δ ($CDCl_3$): 174.6, 165.8, 163.9, 158.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.2, 86.9, 40.7, 24.9, 17.9 ppm. MS (ES^+): 329.7 Da. Anal. ($C_{21}H_{19}N_3O.0.01H_2O$).

Cyclopentanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (24).

Yield 69%, white solid. mp.: 126.5-127° C. ^{1}H-NMR δ ($CDCl_3$): 8.60 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.32-8.26 (m, 3H, phenyl-H+NH), 7.53-7.50 (m, 6H, phenyl-H), 2.77-2.65 (m, 1H, —$CHCH_2CH_2CH_2CH_2$—), 1.98-1.60 (m, 8H, —$CHCH_2CH_2CH_2CH_2$—)ppm. ^{13}C-NMR δ ($CDCl_3$): 175.9, 165.8, 158.4, 137.4, 137.1, 130.7, 130.6, 128.7, 128.4, 128.0, 127.4, 103.2, 46.8, 30.2, 25.9 ppm. MS (ES^+): 343.7 Da. Anal. ($C_{22}H_{21}N_3O.0.04H_2O$).

Cyclohexanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (25).

Yield 87%, white solid. mp.: 142-143° C. ^{1}H-NMR δ ($CDCl_3$): 8.60 (s, 1H, pyrimidinyl-H), 8.57-8.52 (m, 2H, phenyl-H), 8.34 (bs, 1H, NH), 8.30-8.25 (m, 2H, phenyl-H), 7.53-7.49 (m, 6H, phenyl-H), 2.31-2.18 (m, 1H, —$CHCH_2CH_2CH_2CH_2$—), 1.97-1.30 (m, 10H, —$CHCH_2CH_2CH_2CH_2CH_2$—)ppm. ^{13}C-NMR δ ($CDCl_3$): 175.7, 165.8, 163.8, 158.4, 137.1, 130.7, 130.6, 128.6, 128.3, 127.3, 113.6, 103.2, 46.4, 29.2, 25.3 ppm. MS (ES^+): 357.7, 358.7 Da. Anal. ($C_{23}H_{23}N_3O.0.15H_2O$).

TABLE 1

Elemental Analysis

Compound		Elemental Analysis		
No.	Molecular formula	C %	H %	N %
13	$C_{20}H_{17}N_3O.\frac{0.25}{0.025}H_2O$ Calc.	77.61	4.81	11.80
	Found	77.61	5.07	11.88
14	$C_{18}H_{15}N_5O.\frac{0.5}{0.05}EtOH$	74.13	5.18	14.41
		74.06	5.37	14.40
15	$C_{19}H_{17}N_3O$	75.23	5.65	13.85
		75.32	6.23	14.04
16	$C_{20}H_{19}N_3O.\frac{1}{0.1}H_2O$	75.10	6.07	13.14
		75.09	6.29	13.28
17	$C_{20}H_{19}N_3O.\frac{1}{0.1}H_2O$	75.26	6.00	13.16
		75.24	6.20	13.47
18	$C_{21}H_{21}N_3O$	76.13	6.34	12.69
		76.34	6.71	12.88
19	$C_{22}H_{23}N_3O.\frac{1}{0.1}H_2O$	76.10	6.68	12.10
		76.02	6.87	12.35
20	$C_{21}H_{21}N_3O$	76.13	6.34	12.69
		76.25	6.72	12.92
21	$C_{21}H_{21}N_3O$	76.11	6.39	12.68
		75.79	6.62	12.79

TABLE 1-continued

Compound No.	Molecular formula	Elemental Analysis C %	H %	N %
22	$C_{22}H_{28}N_2O$	76.49 76.77	6.71 6.81	12.16 12.56
23	$C_{21}H_{26}N_2O \cdot 0.01H_2O$	76.53 76.16	5.81 6.21	12.75 12.94
24	$C_{22}H_{28}N_2O \cdot 0.04H_2O$	76.78 76.40	6.15 6.56	12.21 12.31
25	$C_{23}H_{28}N_2O \cdot 0.15H_2O$	76.70 76.47	6.44 6.84	11.67 11.85

Biology

A primary function of certain cell surface receptors is to recognise appropriate ligands. Accordingly, we performed radioligand binding studies to establish the degree to which the compound binds to the receptor.

Radioligand Binding Studies [^{3}H]DPCPX was purchased from Amersham. All compounds made were tested in radioligand binding assays to determine their affinities at the human adenosine A_1 receptor. The affinities at the A_1 receptors were determined on CHO cells expressing the human receptors, using [^{3}H]DPCPX as the radioligand according to a previously described method.[9]

Data Analysis Competition binding data were fit to a single-site binding model and plotted using the software package Prism (Graph Pad, San Diego, Calif., USA). The Cheng-Prusoff equation K_i=IC_{50}/(1+[I]/K_d) was used to calculate K_i values, where K_i is the affinity constant for the competing ligand, [I] is the concentration of the free radioligand, and K_d is the affinity constant for the radioligand.

Structure Activity Relationships

In Table 2 results of the radioligand binding assays at the A_1 receptor are displayed, the substituents are defined hereinabove and below with reference to the compound of general formula (II). The reported literature focuses generally on bi-, and tri-cyclic heterocycles as the core structure about which substituents/substituents are varied. This monocyclic core with the 2,4,6-trisubstitution pattern has surprising efficacy at the adenosine A_1 receptor, as can be seen in Table 2. The compounds shown in Table 2 were also tested at the adenosine A_{2A} and A_3 receptors and were shown to be generally selective for the adenosine A_1 receptor.

TABLE 2

Comp	R	Radioligand Binding Assay A_1[a]
13	Ph	671 ± 113
14	CH_3	37.5 ± 8.1
15	CH_2CH_3	9.50 ± 4.6
16	$(CH_2)_2CH_3$	17.6 ± 5.3
17	$CH(CH_3)_2$	11.1 ± 6.2
18	$CH_2CH(CH_3)_2$	14.8 ± 2.7
19	$CH(CH_3CH_3)_2$	6.35 ± 0.4
20	$CH(CH_3)CH_2CH_3$	2.22 ± 1.1
21	$C(CH_3)_3$	27.7 ± 6.2
22	$CH_2C(CH_3)_3$	8.75 ± 4.1
23		6.49 ± 2.2

TABLE 2-continued

Comp	R	Radioligand Binding Assay A_1[a]
24		2.14 ± 0.07
25		15.5 ± 8.4

[a]Displacement of specific [^{3}H]DPCPX binding in CHO cells expressing human adenosine A_1 receptors. K_i (nM) ± SEM (n = 3).

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